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ELECTRODES FOR FUNCTIONAL NEUROMUSCULAR STIMULATION

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THIS QPR IS BEING SENT TO YOU BEFORE IT HAS BEEN REVIEWED BY THE STAFF OF THE NEURAL PROSTHESIS PROGRAM.

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A. CLINICAL COLLABORATION

(QPRs #1, 4, 8, 9)

The original goals of our clinical collaboration were to identify areas where electrode technology was insufficient in meeting clinical needs, to develop performance specifications for the nerve cuff technique of selective muscle activation, and to facilitate timely clinical deployment of the electrodes developed during the contract award.

In the last three years, we have held several meetings with our primary collaborators from both the upper and lower extremity research teams. In those meetings, we provided our collaborators with updates on our research efforts and progress with cuff electrodes and discussed with them the possibilities for future clinical implementation of those electrodes. Included in those discussions were details of possible implant sites, likely patient populations, coordination of regulatory efforts, and compatibility of the cuff electrodes with currently available equipment (stimulators, etc.).

In addition to our primary collaborator meetings, we organized an ad hoc session at the Motor System IV conference held in Deer Creek, OH in 1994. At that session, researchers from around the field were asked to air their concerns and limitations with current electrode designs. Over 100 researchers participated in the ad hoc session, their comments were recorded and summarized for report in QPR #4.

Our original contract proposal called for yearly meetings with our secondary collaborators. However, as these secondary collaborators are active participants in the neural prosthesis community, our professional contact with them and their research was frequent. It seemed of limited benefit and excessive cost and time commitment to organize specific meetings in Cleveland with these collaborators and no such meetings were held during the contract period. Additionally, we recognized that the formulation of specific clinical feasibility studies for these cuff electrodes would require a close collaborative effort, both in geography and in familiarity with the collaborator's current research. We felt that our primary collaborators better fit this ideal, and focused our collaborative efforts with them.

B. ELECTRODE DESIGN AND FABRICATION

Our primary objectives in this section were to develop multiple contact spiral nerve cuff electrodes and to establish their safety and reliability for chronic implantation on peripheral nerve trunks. Multiple electrode designs were pursued, including a conventional foil and wire 12-contact spiral, a new helical spiral cuff design, and an electrode based on thin film techniques. Methods to wind multiple conductor lead cables and alternative means to attach lead wires to foil were studied. In vitro testing of electrodes was conducted, with subsequent analysis of the electrode contacts for corrosion. Additionally, during this contract award we undertook an investigation of new materials to be used in the fabrication of cuff electrodes.

B.1a Multiple Conductor Helical Lead Cables

(QPR #1)

Because of our experience with intramuscular electrodes, we have a well-developed system to wind electrode lead cables comprised of one or two wires. That system uses a tension motor to feed bulk wire onto a spinning mandril to form the helical cable. However, the multiple contact nerve cuffs we investigated in this contract require several lead wires, typically from 4-12. In trying to wind lead cables of more than two wires using the original system, we found that while the motor would maintain the specified total tension, the tensions on the individual wires would vary, producing poor quality cables that were loose and uneven.

We devised a modified winding system for multiple lead cables that relied on individual hanging weights attached to the ends of each wire to provide consistent tension. A stiff, steel spring with 8 coils was mounted onto the carriage of the winder and acted to convert the vertical force of the weights into a horizontal tension and to keep the wires separated as they were fed onto the winder. We have used this system successfully to wind helical lead cables consisting of four individual lead wires.

B.1b Multiple Contact Spiral Nerve Cuff Electrodes

(QPR #2)

We developed and implemented a method to produce silicone rubber spiral nerve cuff electrodes containing twelve individually addressable platinum electrode contacts. The spiral nerve cuffs were fabricated by modifying the method of Naples *et al.* [1988] to create a tri-layer silicone rubber cuff that included 4 longitudinal tripoles of recessed 1 mm diameter platinum dot electrodes, each with a separate lead. A tri-layer approach involving 2 separate lamination steps was required in order to produce these cuffs with accurate

During the contract award, we undertook an investigation of an alternative electrode design, the helical spiral cuff, that is much narrower than the traditional spiral cuff, and has contacts spaced in a linear pattern. These linearly arrayed contacts form tripoles as the cuff wraps around the nerve trunk, with each of the three contacts of a tripole being located in separate "wraps".

inter-contact spacing and adequate sealing of the silicone rubber around the insulated lead wires. The diameters of the cuffs were between 2.5 and 3.5 mm to fit the range of diameters measured for the cat sciatic nerve [Veraart *et al.*, 1993]. These cuffs were used for both acute and chronic animal studies, as described in Section C.

B.1c Fabrication of Helical Spiral Cuff Electrodes
(QPR #2)

Fabrication of the helical spiral is very similar to that of the spiral cuff. Because of the helixing action of the cuff, special attention must be paid to both the stretch percentage and to the angle at which the cuff is oriented relative to the direction of stretch. Modifications to the fabrication protocol to improve the

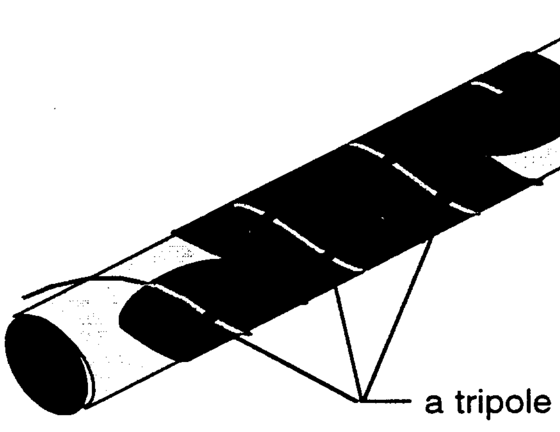

Figure 2: The helical-spiral cuff shown positioned around a nerve.

resulting curl included using smaller diameter wires and eliminating the unstretched layer of silicone rubber sheeting. Equations for both the applied stretch and the angle of orientation of the wires and electrode contacts were established.

Helical spiral cuffs were fabricated and used in a number of acute and chronic animal procedures, as described in Section C.

B.1d Thin Film Fabrication Techniques

(QPR #2)

In the original proposal we specified that we would purchase thin film electrode substrates from Patrick van der Puije at the University of Ottawa. Due to some personnel changes, Dr. van der Puije was unable to provide electrodes in the timeframe we desired. Dr. Stuart Cogan at EIC Laboratories was then identified and contacted as a potential source for thin film electrodes. Dr. Cogan has developed techniques, under NIH SBIR support, to deposit and pattern metallization (titanium/platinum and titanium/iridium) on Teflon substrates. Although we did spend some effort designing and fabricating a mask pattern for 12-electrode spiral cuffs and 12-electrode helical spiral cuffs, we were never able to arrange for fabrication and delivery of these electrodes.

B.2 Electrode Testing

Techniques to Attach Lead Wires to Bonding Pads

(QPR #1, 3)

The goal of this sub-project was to investigate conductive epoxy as a means to attach lead wires to thin-film metallic bonding pads. A study was completed that was designed to test the mechanical and electrical properties of the epoxy after being exposed to simulated accelerated in vivo conditions. Stainless steel rods were bonded end to end with silver impregnated epoxy and were left at room temperature for 2 days. Control samples were tested after an additional 5-7 days at room temperature and aged samples were tested after an additional 5 days in a 79° C saline bath. For those samples that had been aged, ultimate tensile strengths were decreased by 53.7% compared to controls and resistances were increased by 11.7 kΩ relative to initial values. Microscopic examination of the fracture surfaces indicated that cohesive failures were associated with the control samples while adhesive failures were associated with the aged samples. The results from this small-scale study suggested the epoxy experiences degradative changes upon exposure to simulated in vivo conditions. No further investigations of the conductive epoxy were performed.

Testing for Insulation Integrity

(QPR #4)

A simple model was designed and tested for determination of small flaws in the fluoropolymer insulation of lead wires. These small flaws may go undetected by visual and microscopic examination, but could potentially lead to accelerated corrosion of the underlying wire when stimulus currents are applied.

The model was developed around two simple hypotheses: that leakage current at the site of the flaw should be detectable using a relatively low sensitivity ampmeter and that hydrogen should evolve at the site of electrolyte contact (i.e. the site of the flaw) when the wire is driven cathodically. In most cases, both leakage currents and bubble formation were found with intentionally defected wires, although only leakage currents were noted for the smallest defects. The control sample had no detectable leakage current or bubble formation.

Corrosion Testing of Cuff Electrodes

(QPR #4-7)

To investigate their resistance to corrosion, three 12-contact spiral cuff electrodes were stimulated continuously for 10 weeks while submerged in individual flasks containing phosphate buffered saline solution. Microscopic analysis of the contacts of the cuffs was performed and revealed that while the fabrication technique led to some damage to the contacts, including weld-related events and physical damage by the window cutting, the contacts performed without failures. In cases where the charge densities exceeded our expectations of 20 $\mu C/cm^2$, and may have been as high as 100 $\mu C/cm^2$, corrosion pitting of the platinum foil was observed. In all other cases, no evidence of corrosion or metal loss of the contacts was seen.

B.3 Electrode Materials

(QPR #8-11)

A series of in vivo tests in rats was performed to test the biological response to alternative silicone rubber and fluoropolymer materials proposed for use in the manufacture of electrodes.

Segments of wire with 2 different fluoropolymer insulation materials (FEP: original, PFA: alternative) were implanted subcutaneously on the backs of 18 rats. Tissue surrounding the implants was harvested 2 and 4 weeks after implant and evaluated histologically for any difference in the cellular response. No difference in response between the two materials was noted, and we determined that the alternative insulation material was suitable for continued use and investigation.

Spiral nerve cuffs fabricated from 3 different silicone rubber formulations (Silastic Q7-4550: original, NuSil MED2-6400: alternative, NuSil MED2-6641-1: alternative) were implanted bilaterally on the sciatic nerves of 18 rats. Encapsulation tissue surrounding the implants and lengths of the sciatic nerves were harvested 2 and 4 weeks after implant. The encapsulation tissue was evaluated histologically and we determined that the cellular response was improved for both alternative silicone rubber material as compared to the original material. The neural tissue was also evaluated histologically and through electron microscopy. While no difference was noted between nerves with cuffs of different materials, 11 of the 36 nerves demonstrated localized loss of myelin. This myelin loss and the pattern of nerve damage prompted an additional study of rats that is described in Section C.5.

Based on the results of this study, we have proceeded to use wires insulated with PFA fluoropolymer for the leads wires of both our intramuscular and nerve cuff electrodes. PFA is more readily available and has improved processing properties that make it an attractive alternative. Additionally, silicone rubber sheeting made from NuSil materials, particularly MED2-6400, are used routinely in the fabrication of our nerve cuffs.

C. ASSESSMENT OF ELECTRODE PERFORMANCE IN AN ANIMAL MODEL

The aim of the work to be performed in this section was to demonstrate that the multicontact cuff electrode can be used, over a long period of time, to activate selectively and independently separate compartments of a large nerve that serves several muscles. Through both acute and chronic animal experiments, we evaluated the performance of spatially selective nerve activation with the multiple contact nerve cuff electrode. Our specific performance goals were (i) to activate selectively and progressively individual regions of a large nerve trunk; (ii) to activate muscles in a graded and controlled manner over their full range of force production; and (iii) to activate muscles in a stable and length-independent manner.

C.1a Performance Testing in Acute Animal Experiments

<u>Spiral Cuff Electrodes</u>

QPR #2

The acute experiments were designed to determine the level of selectivity achievable for five individual muscles innervated by the sciatic nerve. The methods used were described in detail in a manuscript entitled "Non-invasive measurement of the input-output properties of peripheral nerve stimulating electrodes" published in the Journal of Neuroscience Methods, 65(1996) 43-50. The abstract from that publication is as follows:

A non-invasive method was developed to determine the input-output (I/O) properties of peripheral nerve stimulating electrodes. An apparatus was fabricated to measure the 3-dimensional (3-D) isometric torque generated at the cat ankle joint by electrical activation of the sciatic nerve. The performance of the apparatus was quantified, and the utility of the method was demonstrated by measuring the recruitment properties of multiple contact nerve cuff electrode. Torque-twitch waveforms, recruitment curves of peak torque as a function of stimulus current amplitude, and 2-D joint torque vectors were used to analyze the recruitment properties of the cuff. The peak of the twitch torque was an accurate measure of excitation even for muscles having fibers with varying speeds of contraction. The evoked twitch waveforms and torque vectors generated by selective stimulation of individual nerve branches with a hook electrode were compared to those produced by stimulation of the nerve trunk with the cuff electrode. These data allowed determination of the regions of the nerve trunk that were activated by different electrode geometries and stimulus parameters. The positional stability of electrode recruitment properties could be quantified by measuring I/O characteristics at different limb positions. The methods described are useful for characterization of neural stimulating electrodes and for studies of motor system physiology.

Helical Spiral Cuff Electrodes

QPR #4

Helical-spiral nerve cuff electrodes containing two sets of tripoles were used in a number of acute animal procedures. In those experiments, we found that we could control dorsiflexion and plantarflexion with both monopolar and tripolar electrode configurations employed through the helical spiral. These results were very encouraging, as they suggested that a 12-contact electrode of 4 tripoles could possibly be replaced with a 4-contact electrode of all monopoles. This change in electrode contact number would have positive implications for cuff manufacture, lead configuration and manufacture, electrode safety due to reduced bulk of the implant, and stimulator design due to the reduced number of required channels. Chronic implants of the helical spiral design were pursued, as described in the following section. In addition, a series of investigations were initiated to explore the differences between monopolar and tripolar stimulation, as described in sections B./C./D.

C.1b Performance Testing in Chronic Animal Experiments

QPR #7,8

The chronic experiments were designed to investigate the safety, efficacy, and reliability of our electrodes and stimulation techniques, the possible role of the electrode leads in mechanically induced nerve trauma, the impact of removal and replacement of encapsulated cuff electrodes, and the trauma resulting from implantation of cuff electrodes.

Computer Controlled Laboratory Stimulator

(QPR #2)

A stimulator (LABSTIM), specifically designed to be controlled by a personal computer, was developed to improve the efficiency of the stimulation portions of our animal experiments. The stimulator proved to be of invaluable assistance for not only the chronic animal experiments, but the acute procedures as well. A sequence of coded pulses, transmitted via two input/output digital lines, determine all stimulation parameters. Pulse width, frequency, and amplitude of stimulation can be preset by the computer. Pulse parameters can also be updated during stimulation, which allows the generation of a burst of stimuli with gradually changing pulse widths, frequencies, or amplitudes. Pulse width range is 10 µsec - 10 msec, and the range of frequency is 0.1 Hz - 1 KHz. The maximum amplitude that can be generated by the stimulator is 25 mA.

This system was originally interfaced with a Macintosh IIfx; it has since been modified to interface with a Macintosh Quadra and now with a PC (Gateway 2000). A menu driven software interface was developed to provide the required communication protocol for transmission of parameter values to the stimulator. This program uses the Labview software package and two computer boards (I/O and timer boards) all manufactured by National Instruments. The program has been expanded to include data acquisition and analysis as well. Hence, the same program can now control stimulation as well as data collection simultaneously. The present program can handle communications for an eight channel stimulator.

Spiral Cuff Electrodes

Chronic cuff electrode experiments were performed on 7 adult felines, with the duration of the implants ranging from 28-34 weeks. Two abstracts have been published and a manuscript has been submitted for publication describing the results of this set of chronic experiments.

Temporal Stability

An abstract entitled "Temporal stability of nerve cuff electrode recruitment properties" was published in the Proceedings of the 17th Annual Conference of the IEEE-EMBS, Montreal, 1995. The text of that abstract follows:

The recruitment properties of multiple contact nerve cuff electrodes chronically implanted on the cat sciatic nerve were measured, and the week to week variability was documented. The variability in recruitment properties was greatest between 1 week and 8 weeks post-implant. After 8 weeks the session to session changes were significantly smaller than in the early post-implant period. No trends were observed in the recruitment patterns that would suggest any damage to the nerve occurring during the implant period. These results suggest that the implant is safe and that tissue encapsulation acts to stabilize the cuff electrode and prevent relative movement between the cuff and the nerve trunk. This study, combined with previous studies, demonstrates that multiple contact spiral nerve cuff electrodes can be used in long-term implants to activate discrete regions of peripheral nerve trunks.

Positional Dependence of Recruitment

An abstract entitled "Positional dependence of the recruitment properties of nerve cuff stimulating electrodes" was published in the Proceedings of RESNA, June 1995, 717-719. The text of the abstract follows:

Changes in the recruitment properties of a multiple contact nerve cuff electrode at different limb positions were measured in an animal model. Immediately after implantation, the recruitment properties changed with limb position indicating that the cuff was moving relative to the nerve fibers. After 8 weeks of implantation, sufficient time to allow fibrous tissue encapsulation of the electrode, the recruitment properties were no longer dependent on limb position. This suggested that tissue encapsulation acted to stabilize the cuff electrode, eliminating any position dependent recruitment properties. This is an advantage over presently used muscle-based electrodes. Stable input-output properties should simplify user control of motor prosthetic devices and thus improve function.

Stability of Chronic Cuff Implants

A manuscript entitled "Stability of chronically implanted multiple contact nerve cuff electrodes" was prepared and submitted for publication in IEEE Transacations on Rehabilitation Engineering. Revisions to the manuscript are in process. The abstract of this submitted manuscript follows:

The objective of this investigation was to measure the recruitment characteristics of chronically implanted nerve cuff electrodes as a function of implant time and limb position. Silicone rubber spiral nerve cuff electrodes, containing 12 individual platinum electrode contacts, were implanted on the sciatic nerve of 7 adult cats for 28-34 weeks. Recruitment curves of ankle joint torque as a function of stimulus current amplitude were used to evaluate the temporal and positional stability of electrode input-output characteristics. Torque-current curves were extremely repeatable within an experimental session, but there were changes between measurement sessions. The degree of variability differed greatly between electrodes and between different contacts within the same electrode. Torque-current curves were parameterized by determining the currents required to generate 20%, 50% (I50) and 80% of the maximum torque. The largest changes in the current parameters were measured between 1 week and 8 weeks post-implant. After 8 weeks, there was no significant trend in I50, and the session to session changes in I50 were small ($6 \pm 13\%$). Measurements of torque-current curves at different ankle joint angles indicated that the recruitment properties of encapsulated cuff electrodes did not depend on limb position. These results indicate that multiple contact spiral nerve cuff electrodes can be used in long-term implants to activate discrete regions of peripheral nerve trunks.

Neural and Connective Tissue Response
(QPR #8)

The purpose of this project was to document the tissue response to long-term presence of multiple contact spiral nerve cuff electrodes Spiral nerve cuff electrodes, containing 12 individual platinum electrode contacts, each with its own lead, were chronically implanted on the right sciatic nerve of 7 adult cats for 28-34 weeks.

All animals maintained normal activity patterns for the duration of the implant. All animals except one (#946) were walking normally within 24 hours after implant, and thereafter maintained normal mobility and behavior. Cat 946 exhibited a "drop foot" in the implanted leg characterized by external rotation of the paw and dragging of the toes during walking. This condition appeared most severe 2 days after implant, and improved steadily thereafter. The toes no longer dragged 7 days post-implant, and gait was entirely normal by 12 days post-implant. In all other cases observation indicated normal gait patterns and the neurological tests revealed no abnormalities.

At the time of explant the cuff and lead cable were surrounded by fibrous tissue encapsulation. The connective tissue layer between the cuff and the nerve was 50-300μm thick and consisted of fibroblasts, collagen, and leukocytes. The outer encapsulation ranged from 50μm to 1mm thick, and consisted of a higher proportion of collagen and inactive fibroblasts, and fewer leukocytes than the inner encapsulation tissue. The response at the end of the cuff was typically the region that showed the thickest encapsulation tissue.

In four cases the cuff had a spiral configuration around the outside of the nerve trunk. In one case the inner edge of the cuff had moved through the epineurium such that two small fascicles lay between the innermost and second wraps of the cuff. In two cases the cuff was in a "double-barrel" configuration at the time of explant.

All nerve sections 2 cm proximal to the cuff appeared normal. At the level of the cuff, small regions of one fascicle in each of two nerves exhibited abnormal appearance. Morphological changes included thinly myelinated axons, proliferation of endoneurial connective tissue, and perineurial thickening. In both cases the nerves looked normal distal to the cuff indicating that the changes were localized to small regions within the cuff. Three of the seven implants exhibited morphological changes distal to the cuff electrode, however, the cuff-level sections and proximal sections of these 3 nerves all appeared normal. Morphological changes were characterized by perineurial thickening, scattered thinly myelinated axons, proliferation of endoneurial connective tissue, and an apparent increase in the ratio of small diameter nerve fibers to large diameter nerve fibers.

Analysis of Chronically Implanted Electrodes
(QPR#8)

Spiral nerve cuff electrodes used in chronic animal experiments were evaluated for evidence of corrosion. The electrode contacts were removed from the silicone rubber and examined with both light and electron microscopes. No corrosion was found on any contacts from the chronically implanted electrodes. Observations of the condition of the platinum foil contacts and weld zones were otherwise similar to those made with the in vitro electrodes. In one instance, corrosion was found on a single strand of wire welded to a platinum contact. From these observations, it can be concluded that in general, the platinum foil contacts are not readily corroded by the in vivo environment. It should be remembered, however, that only limited stimulation was applied through these cuffs during the implantation period.

Helical Spiral Cuff Electrodes
(QPR#4, 6)

Six helical-spiral nerve cuff electrodes were implanted on the left sciatic nerve of six animals for a 6-9 month period. Of the six implants, in only one animal was the cuff found to be properly positioned around the nerve at the end of the implantation period. In two of the animals, only a single wrap of the cuff was found to be positioned around the nerve while in the remaining three animals, the cuffs were completely off the nerve. Of these three implants, one cuff was adjacent to the nerve trunk while the other two cuffs were found in the subcutaneous space.

Three acute procedures were performed to investigate whether the helical spirals were displaced from the nerve shortly after implant. After the cuff was placed on the nerve, the animal's hind limb was moved over the full range of motion. However, in none of the 3 animals did the cuff become displaced. We then proceeded to perform another 2 chronic implants in which x-rays were taken periodically to document the time course of the cuff dislodgment. Small, very flexible cuffs, embedded with iron powder to make them clearly visible on the x-ray film, were placed on either side of the helical spiral cuff implant. Unfortunately, it was these 'marker' cuffs that displaced from the nerve, and not the helical spirals.

While the mechanism for dislodgment is still unclear to us, we have theorized that the helical spirals we designed and used were too flexible. We did not pursue this electrode design any further during this contract award. However, we do believe that the electrode has potential for success and presents unique advantages to the spiral cuff design. Our limited histological evidence showed no signs of neuronal abnormalities, suggesting that further studies of the helical spiral design are warranted.

C.1c Quantitative Analysis of Electrode Performance

(QPR #2,3)

Our objectives in this section were to demonstrate our ability to activate selectively and progressively individual regions of a large nerve trunk, activate muscles in a graded and controlled manner over their full range of force production and activate muscles in a stable and length-independent manner.

The methods used in these investigations were described in a manuscript entitled "Non-invasive measurement of the input-output properties of peripheral nerve stimulating electrodes" published in the Journal of Neuroscience Methods, 65: 43-50, (1996). The abstract from that publication was provided in section C.1a.

The results of the study, including recruitment curve and selectivity measures, were described in a manuscript entitled "Quantification of recruitment properties of multiple contact cuff electrodes" published in IEEE Transactions on Rehabilitation Engineering, 4(2): 49-62, (1996). The abstract of that publication is as follows:

Nerve-based stimulating electrodes provide the technology for advancing the function of motor system neural prostheses. The goal of this work was to measure and quantify the recruitment properties of a 12 contact spiral nerve cuff electrode. The cuff was implanted on the cat sciatic nerve trunk, which consists of at least four distinct motor fascicles, and the torque generated at the ankle joint by selective stimulation of the nerve was recorded in nine acute experiments. Comparisons of torques generated with the cuff to torques generated by selective stimulation of individual nerve branches indicated that the cuff allowed selective activation of individual nerve fascicles. Selectivity was dependent on the relative location of the electrode contacts and the nerve fascicles, as well as the size and relative spacing of neighboring fascicles. Selective stimulation of individual nerve fascicles allowed independent and graded control of dorsiflexion and plantarflexion torques in all nine experiments. Field steering currents improved selectivity as reflected by significant increases in the maximum torques that could be generated before spillover to other fascicles, significant increases in the difference between the current amplitude at spillover and the current amplitude at threshold, and significant increases in the slope of the current distance relationship.

C.2 Role of Leads in Mechanical Trauma to Peripheral Nerves

In this section, our aim was to determine whether contacts and lead wires contribute to mechanically induced neural damage. A number of chronic implants were proposed, but were not implemented. Cuffs with and without leads were included in the study of alternate electrode materials described in section B.3 and performed on rats. In that study, no correlation between the observed neural trauma and the presence of the cuff lead was established. We determined, based on these results and the results of our initial chronic cat studies, that the costs and time required to implement this study were unwarranted.

C.3 Removal and Replacement of Encapsulated Spiral Cuff Electrodes (QPR #9)

The purpose of this project was to establish the feasibility of surgical removal of encapsulated spiral nerve cuff electrodes and subsequent replacement with a second electrode. A number of experiments were proposed, but only 1 such experiment was carried out. In that cat, bilateral cuff implants were allowed to encapsulate for 4 weeks. A second surgical procedure was then performed in which the encapsulated cuff was exposed and isolated, the encapsulation tissue was incised to create a flap, the spiral cuff electrode was removed from the nerve through this flap, and another cuff was then placed around the nerve trunk within the original encapsulation tissue. This proved to be easily performed, with minimal apparent manipulation or mechanical trauma inflicted to the nerve trunk on either limb of the animal. As this single experiment was without complication, no further studies were deemed necessary.

C.4 Surgical Trauma During Implantation of Multiple Contact Cuff Electrodes

(QPR #11, 13)

Short term chronic studies, lasting ten days, involving monopolar cuff electrode implants were carried out to investigate the effects of the surgical procedure and those due to the short-term presence of the cuff and leads on axon viability. A sham procedure was performed on the animal's right limb, while a normal cuff implant was performed on the animal's left limb. At the conclusion of the 10 day period, each animal was sacrificed by aortic perfusion and the tissue was excised for histological processing. In one animal, the nerve cuff was found subcutaneously at the site of the initial incision. In a second animal, the nerve cuff was found to lie between the muscle planes adjacent to the nerve trunk. In the remaining two animals, the cuffs were found in place on the nerve. Immature encapsulation tissue was found surrounding the cuff implants. Axonal or neural abnormalities were not found at proximal, cuff or distal levels in any of the 8 nerves. Axonal density was found to be consistent and uniform throughout the sections. Leukocytes were not seen within the fascicles, nor was there evidence of myelin degradation, fibrosis or Schwann cell proliferation.

From this series of four cats, no insult to the nerve was observed, indicating that neither the implant procedure nor the presence of the cuff during the 10 day maintenance period resulted in neural injury. Further investigations of the degree of surgical trauma resulting from cuff implant were performed in a series of animal experiments described in section C.5.

C.5 Tissue Injury Resulting From Cuff Electrode Implantation

(QPR #15 and manuscript)

The work performed in this section was an addition to our original workscope and was initiated due to the results observed in section B.6. The study was designed to investigate the mechanisms for the characteristic subperineural region of neuronal changes that are found in a consistent percentage of chronic cuff implants. A manuscript detailing the methods and results of the study has been prepared. The abstract and working title of this manuscript are provided below.

Tissue Damage and Spiral Nerve Cuff Electrodes: An Investigation of Surgical Trauma and Possible Free Radical Effects

Abstract

Studies of nerve cuff electrode implants conducted in our lab and others have found that approximately 30% of the cuffed nerves contain localized regions with thinning or absent myelin sheaths surrounding apparently intact axon fibers. We have speculated that the surgical intervention required for cuff implant disrupts the local blood supply to the nerve, resulting in focal ischemia and subsequent free radical mediated damage to the myelin, while leaving the axons largely intact. In this study, we attempt to distinguish the effects on the nerve of the surgical procedure alone as compared to the chronic presence of the implanted cuff. Additionally, the effectiveness of alpha-tocopherol (vitamin E), a known free radical scavenger, in preventing the damage to the myelin was studied. Sham and complete cuff electrode implants were performed bilaterally on the sciatic nerves of 36 rats, half of which had been fed elevated levels of vitamin E. Two weeks after implant, the rats were killed and nerve tissue at the sites of the experimental procedures was excised for histological processing. Through light and electron microscopic evaluation, no increase in morphological nerve fiber changes were observed for those nerves that had a cuff implant compared to those that had a sham implant. This is consistent with our theory that it is the implant procedure itself that has the greater potential to effect the nerve than does the presence of the cuff around the nerve. Although higher levels of Vitamin E were found in tissues and plasma of animals fed the elevated diet, no difference in overall histological response was seen between the animals fed the different concentration chow.

B. ELECTRODE DESIGN AND FABRICATION

C. ASSESSMENT OF ELECTRODE PERFORMANCE IN AN ANIMAL MODEL

D. MODIFICATIONS TO IMPROVE FUNCTIONAL PERFORMANCE

Comparison of Monopolar and Tripolar Recruitment Characteristics

(QPR #9, 10)

In order to reduce the number of lead wires and improve the clinical feasibility of the nerve cuff electrode, we investigated a simplified cuff configuration that required only four lead wires and contained monopoles, rather than tripoles. Monopolar cuff electrodes produce virtual anodes at the cuff edges. With a cuff of the same length as a longitudinally spaced tripole, the monopole cuff and its respective virtual anodes have a current flow similar to that produced by the tripolar configuration. The data from two animal experiments indicate that monopolar cuff electrode stimulation can generate a comparable recruitment range as that generated with the tripolar configuration. These results have encouraged us to continue to pursue this simplified cuff configuration in our current and future studies.

C. ASSESSMENT OF ELECTRODE PERFORMANCE IN AN ANIMAL MODEL

D. MODIFICATIONS TO IMPROVE FUNCTIONAL PERFORMANCE

Effects of Pulse Duration on Selectivity

(QPR #6)

In our efforts to improve the functional performance of the spiral cuff electrode, we undertook a study to investigate the effects of pulsewidth on selectivity and tested our hypotheses in both computer simulations and in animal studies. A manuscript entitled "The effect of stimulus pulse duration on selectivity of neural stimulation" detailing this work was published in IEEE Transactions on Biomedical Engineering, 43(2): 161-166 (1996). The abstract from this publication follows:

Choice of stimulus parameters is an important consideration in the design of neural prosthetic systems. The objective of this study was to determine the effect of rectangular stimulus pulsewidth (PW) on the selectivity of peripheral nerve stimulation. Computer simulations using a cable model of a mammalian myelinated nerve fiber indicated that shorter PW's increased the difference between the threshold currents of fibers lying at different distances from an electrode. Experimental measurements of joint torque generated by peripheral nerve stimulation demonstrated that shorter PW's generated larger torques before spillover and created a larger dynamic range of currents between threshold and spillover. Thus, shorter PW's allowed more spatially selective stimulation of nerve fibers. Analysis of the response of a passive cable model to different duration stimuli indicated that PW dependent contributions of distributed sources to membrane polarization accounted for the observed differences in selectivity.

D. MODIFICATIONS TO IMPROVE FUNCTIONAL PERFORMANCE

D.1.b Simulation of Selective Inactivation of Peripheral Fibers

(QPR#5)

Our aims in this project were to investigate novel stimulus waveforms as a means to activate selectively the fibers lying deep in a nerve trunk without activating the fibers near the surface. Computer simulations and acute animal experiments were performed to pursue our goals. The results of these studies are described in a manuscript entitled "Inversion of the current-distance relationship by transient depolarization" that was published in IEEE Transactions on Rehabilitation Engineering 44: 1-9, (1997). The abstract of that publication follows:

The objective of this research was to develop a technique to excite selectively nerve fibers distant from an electrode without exciting nerve fibers close to the electrode. The shape of the stimulus current waveform was designed based on the nonlinear conductance properties of neuronal sodium channels. Models of mammalian peripheral myelinated axons and experimental measurements on cat sciatic nerve were used to determine the effects of subthreshold polarization on neural excitability and recruitment. Subthreshold membrane depolarization generated a transient decrease in neural excitability and thus an increase in the threshold for stimulation by a subsequent stimulus pulse. The decrease in excitability increased as the duration and amplitude of the subthreshold depolarization were increased, and the increase in threshold was greater for fibers close to the electrode. When a depolarizing stimulus pulse was applied immediately after the subthreshold depolarization, nerve fibers far from the electrode could be stimulated without stimulating fibers close to the electrode. Subthreshold depolarizing prepulses inverted the current-distance relationship and allowed selective stimulation of nerve fibers far from the electrode.